TITLE
PEPTIDASE-CLEAVABLE, TARGETED ANTINEOPLASTIC DRUGS AND THEIR THERAPEUTIC USE

FIELD OF THE INVENTION

This invention is directed to antineoplastic agents conjugated to enzyme-cleavable peptides comprising the amino acid recognition sequence of a membrane-bound and/or cell-secreted peptidase, and to the use of such conjugated compounds as chemotherapeutic agents in the targeted treatment of cancers.

BACKGROUND OF THE INVENTION

Many anti-tumor compounds are restricted in their use because of their narrow therapeutic index, that is, the toxicities induced when the compounds are administered above certain dose levels outweigh the benefits thereby afforded. Anthracycline (*e.g.* doxorubicin) therapy, for example, is limited in that administration of the drug at levels in excess of cumulative 500 to 550 mg doxorubicin/m^2 produces a substantial risk of cardiotoxicity and myelosuppression (von Hoff, et al.). However, compounds such as doxorubicin often remain the drug of choice for particular forms of chemotherapy; therefore it would be quite useful to develop means of lowering the compounds' toxicities whilst maintaining their therapeutic potential.

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One means of approaching this objective that has been tried for several decades is the design of prodrug molecules that are differentially activated in tumor tissue, that is, drug molecules inactive or significantly less active upon administration that are selectively processed in tumor tissue so as to be therapeutically active therein. Leu-Dox (the amino acid leucine conjugated to the anthracycline doxorubicin), for example, is a prodrug found to require hydrolysis of the amino acid from the prodrug by intracellular proteases in order to release the anthracycline (Boven, et al. (1990)). Conversion of Leu-Dox to Dox in mice occurs rapidly, although incompletely, to approximately 20% overall conversion (de Jong, et al. (1992a)). A similar observation has been made upon administration of Leu-Dox to humans (de Jong, et al. (1992b); Canal, et al.); in a Phase I trial, approximately 25% conversion of Leu-Dox to Dox occurred rapidly in the tumor tissue. Moreover, in a human ovarian tumor xenograft mouse model, Leu-Dox has